GLP-1 and GIP analogues as novel treatments for Alzheimer's and Parkinson's disease

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abstract

Type 2 diabetes is a risk factor for developing chronic neurodegenerative disorders such as Alzheimer's or Parkinson's disease. The underlying mechanism appears to be insulin desensitisation in the brain. A range of GLP-1 mimetics and GIP analogues initially designed to treat diabetes protected transgenic animals that model Alzheimer's disease and toxin based animal models of Parkinson's disease. Novel dual GLP-1/GIP analogues also show good neuroprotective effects. Based on these findings, first clinical trials have been conducted. In a pilot study in patients with Alzheimer's disease, the GLP-1 analogue liraglutide showed good protective effects in ^{18}FDG-PET brain imaging. It was found that the disease related decay of brain activity had been completely stopped by the drug. In a pilot study in patients with Parkinson's disease, the GLP-1 mimetic exendin-4 showed good protection from motor and cognitive impairments. These results demonstrate the potential of developing disease-modifying treatments for Alzheimer's and Parkinson's disease.

Key words: insulin; neurodegeneration; incretins; growth factors;

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1. Diabetes is a risk factor for neurodegenerative disorders

One of the established risk factors for the development of Alzheimer's (AD) or Parkinson's disease (PD) is type II diabetes mellitus (T2DM). In several patient data base analyses, T2DM has been identified as a risk factor for PD, indicating that insulin desensitization in the periphery may be a factor in initiating or accelerating the development of neurodegenerative processes [1,2]. In AD, several epidemiological studies found a correlation between T2DM and an increased risk of developing AD at a later stage in life [3-8]. In one investigation, T2DM had been identified as a risk factor that doubled the chance of developing AD [9]. In a longitudinal cohort study that follows up the health status of people over time, glucose intolerance in a oral glucose tolerance test correlated with an increased risk of developing AD in people with significantly elevated blood glucose levels [10]. Other studies arrived at similar conclusions [11]. In Parkinson's disease, T2DM has also been identified as a risk factor [12-15]. In the basal ganglia, dopaminergic transmission failure, insulin desensitisation and energy depletion had been associated with T2DM [16].

2. Insulin signaling desensitises in the brain

A key mechanism that appears to link T2DM with neurodegnerative disorders is the loss of insulin signaling in the brain. A biochemical analysis of brain tissue of AD patients showed a clear profile of insulin desensitisation, even in people that were not diabetic [17-20]. Insulin receptor subunits and IRS1 was found to be hyper-phosphorylated, a biochemical profile also seen in diabetics in the peripheral tissue [19,20]. In PD, insulin desensitisation was also observed in the key brain area such as the basal ganglia and substantia nigra [1,21,22]. Energy utilisation, mitochondrial function, insulin signaling and dopamine transmission was found to be compromised [21,23,24]. It is interesting to note that these effects were also found in non-diabetic subjects. This demonstrates that insulin desensitisation is not always dependent on glucose levels. However, patient data showed that a higher percentage of PD patients were diabetic or glucose intolerant compared to age matched controls [2].

3. Insulin is a key growth factor

Insulin is an important growth factor that is essential for the homeostasis and cell growth and repair in neurons. Counter-intuitively, glucose uptake in neurons is not insulin dependent, with the exception of large neurons that express the GLUT4 subtype [25,26]. Hence, the brain had been commonly known as an 'insulin insensitive' organ [27]. However, insulin and IGF-1 are important growth factors that activate cell growth, cell repair, gene expression, energy utilisation and protein synthesis [28-31]. This may explain why insulin desensitisation in the brain increases the risk for developing neurodegenerative disorders such as AD and PD.

4. Treating AD patients with insulin

Just as insulin improves T2DM, treating AD patients with insulin shows improvements in cognition, attention, reducing levels of biomarkers for AD, and normalising brain energy utilisation [32-35]. Insulin cannot be given to people who are not diabetic. Delivering insulin by nasal application where it enters the brain more directly can circumvent the problem of inducing hypoglycaemia. Nasal application of insulin improved attention and memory formation even in non-diabetic people [34,36,37]. A phase II clinical trial in AD patients showed improved cognition in patients with mild cognitive impairments (MCI). It further improved the amyloid1-40/1-42 ratio in the cerebrospinal fluid and increased brain activation as seen in ^{18}FDG-PET scans which measure brain activity and energy utilisation, and furthermore showed improvement in mental tasks [38-40]. However, similar to patients with T2DM, insulin delivery appears to enhance brain insulin desensitisation and worsen cognitive decline [40]. For a review, see [41,42].

5. T2DM drugs have neuroprotective properties

Drugs to treat T2DM and that normalise insulin signaling are on the market. These are mimetics of the incretin hormone Glucagon-like peptide 1 (GLP-1) [43,44]. GLP-1 is a growth factor of the glucagon family type and has similar properties than insulin has [31]. These drugs do not affect blood glucose levels directly and therefore are safe to take by people who are not diabetics [45]. The drugs are well received and have a good safety record [46].
Several of these drugs can cross the blood-brain barrier, which demonstrates that there is a transporter for GLP-1, similar to other growth factors such as insulin or leptin [25,47-51].

There has been some discussion whether GLP-1 receptors are expressed in neurons. A study that analysed RNA expression of the GLP-1 receptor has demonstrated a wide distribution of GLP-1Rs in the brain, including the cortex, hippocampus, and the substantia nigra; key brain areas in AD and PD disease development [52]. Several antibody-based histological investigations of GLP-1 receptor expression in the brain had been conducted since [53-59]. However, a study that demonstrated that these antibodies may not be selective for the receptor followed [60], and a recent analysis of GLP-1R expression in the brain using a transgenic GFP expression reporter mouse strain demonstrated good expression of GLP-1Rs in the cortex, hippocampus area CA3 and dentate gyrus, and others [61], putting the discussion to rest once and for all.

6. GLP-1 mimetics show effects in animal models of Alzheimer's disease

In several transgenic mouse models of AD, which expresses the human Swedish mutated form of the amyloid precursor protein (APP) and a mutated human form of presenilin-1 (PS-1), both mutations which lead to AD in humans, GLP-1 mimetics were neuroprotective. Liraglutide (Victoza®) is on the market as a treatment for T2DM [62]. Once-daily injections for 8 weeks reduced key parameters such as memory loss, synapse loss, reduced synaptic transmission, chronic inflammation in the brain, and amyloid plaque load in the brain [63]. The same treatment in aged transgenic mice with advanced amyloidosis still showed some protective effects, suggesting that treatment at later disease stages may still have benefits [64]. When treated from an early age onward, the drug did prevent disease progression and has the potential to be used as a prophylactic [65]. The GLP-1 mimetic lixisenatide (Lyxumia®) also had similar neuroprotective effects compared to liraglutide [66]. Liraglutide had clear protective effects in a mouse model of tau phosphorylation and tangle formation, a key biomarker for AD. In the human P301L mutated tau expressing mouse, a model of fronto-temporal lobe dementia and ALS, liraglutide reduced the amount of tangles and hyperphosphorylated tau [67]. In the accelerated senescence SAMP8 mouse model, liraglutide also showed good protective effects on memory formation and neuronal loss [68]. The GLP-1 mimetic exendin-4 (Byetta®, Exenatide®, Bydureon®) also showed good effects in a triple transgenic mouse model of AD [69].

Exendin-4 showed neuroprotective effects in other animal models of neurodegeneration as well [70-73]. GLP-1 mimetics furthermore improve neuronal progenitor cell proliferation and neurogenesis in the mouse brain. In mouse models of AD and of diabetes, GLP-1 analogues can increase or normalise neuronal progenitor cell proliferation in the CNS [57 50,63,69,74-76]. Testing analogues of the sister incretin Glucose-dependent insulinotropic polypeptide (GIP) also showed good effects in the APP/PS1 mouse model of AD [77-79].

7. GLP-1 mimetics show effects in animal models of Parkinson's disease

Exendin-4 has shown good neuroprotective effects in several mouse models of PD. In the 6-hydroxydopamine (6-OHDA) model of PD where dopaminergic neurons are eliminated by 6-OHDA, animals were treated for 3 weeks and showed functional recovery. In the substantia nigra, dopaminergic neurons were partly protected from the toxic effects of 6-OHDA [80].
This result was confirmed in a second study which also used the 6-OHDA lesion technique, and a second technique, the lipopolysaccaride (LPS) induced substantia nigra lesion. Exendin-4 reduced the lesions induced by the toxins. The levels of dopamine measured in the basal ganglia were also increased. The numbers of neurons in the substantia nigra was also higher than in the lesion only group [81]. In a third study, Exendin-4 protected dopaminergic neurons and rescued motor function in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesion mouse model of PD [59].
When comparing the more effective GLP-1 mimetics liraglutide and lixisenatide with exendin-4, it was found that both liraglutide and lixisenatide demonstrated good protective effects while exendin-4 showed only minor protection in the MPTP mouse model of PD. Motor activity was partly rescued, and dopaminergic neurons were protected in the substantia nigra. Expression of the dopamine biomarker tyrosine hydroxylase (TH) was also rescued in the liraglutide and lixisenatide treated mice. Pro-apoptotic cell signaling was reduced, while growth factor signaling was enhanced by both drugs [82]. When testing the sister incretin GIP in the MPTP mouse model, it was found that the long-lasting protease resistant analogue D-Ala2-GIP-glu-PAL showed good protective effects. Motor activity was partly rescued, and the number of dopaminergic neurons in the substantia nigra was increased. Synapse numbers were increased, and the cAMP/PKA/CREB growth factor second messenger pathway was shown to be activated by D-Ala2-GIP-glu-PAL [83].

New dual GLP-1 and GIP receptor agonists have been developed to treat T2DM. Some have already been tested in clinical trials and show superior performance compared to liraglutide [84]. When testing a novel dual agonist in the MPTP mouse model of PD, it was found that it rescued motor activity, synapse numbers, numbers of dopaminergic neurons in the substantia nigra, and reduced chronic inflammation (see fig. 1). Interestingly, the expression of the neuroprotective growth factor Brain-Derived Neurotropic Factor (BDNF) was enhanced, which can explain some of the neuroprotective effects observed [85,86]. BDNF has clear protective effects on synaptic activity [87,88].

8. Clinical trials

The results obtained in the preclinical studies show an impressive range of neuroprotective effects of GLP-1 and GIP mimetics. As several GLP-1 mimetics are already on the market as treatments for T2DM with a good safety profile, clinical trials have started that investigate the neuroprotective effects of exendin-4 or liraglutide in PD or AD patients.

Parkinson's disease

A clinical pilot trial of exendin-4 in PD patients has been completed (clinical trials identifier NCT01174810). This 'proof of concept' study tested the effects of exendin-4 in a randomised, open label trial in 45 patients. The drug was administered over 12 months, followed by a 2 month wash-out period. In a single-blinded rating of motor activity, clear improvements were found, and cognitive measures were improved in the drug group compared to controls. Exendin-4 treated patients had a mean improvement at 12 months on the MDS-UPDRS of 2.7 points, compared to a mean decline of 2.2 points in control patients ($P = 0.037$). Importantly, the drug group showed a clear improvement in the Mattis DRS-2 cognitive score, suggesting that exendin-4 has beneficial effects on cognition and memory [89]. The group was re-tested 12 months after the trial had finished, and the clear differences between groups in motor performance and cognitive scores had not changed [90]. This suggests that the group difference is not due to a placebo effect, as 12 months is too long for such subjective effects to last.
A phase II trial testing the once-weekly formulation of exendin-4, Bydureon®, has been completed (NCT01971242). The results will be reported shortly and initial observations suggest a good outcome.

A phase II trial testing liraglutide in PD patients is under preparation and will start in July 2016, testing 100 patients in a double blind, placebo controlled design.

Alzheimer's disease

A randomized, double blind clinical trial to assess the safety and efficacy of Exendin-4 treatment in 230 MCI patients (early phase Alzheimer's disease) is currently ongoing at the NIH/NIA in the USA. This trial is testing the effects of exendin-4 on key parameters such as performance in the Clinical Dementia Rating (CDR) scale sum-of-boxes, the Alzheimer's Disease Assessment Scale - cognitive sub-scale (ADAS-cog), Behavioral and cognitive performance measures, changes on structural and functional MRI brain imaging, and hormonal and metabolic changes in cerebrospinal fluid and plasma AD biomarkers (ClinicalTrials.gov Identifier: NCT01255163).

A small-scale trial with 34 patients has been completed in Denmark at the University of Aarhus. This double blind, randomized trial tests the effects of liraglutide vs. placebo on MCI patients, using ^{18}FDG-PET imaging to estimate cortical activity and PIB-PET imaging to measure plaque load [91]. Excitingly, there was a clear effect on brain ^{18}FDG-PET activity. FDG is a modified glucose molecule, and the uptake correlates well with brain activity, synaptic activity, and disease progression [92]. While the placebo group showed the expected reduction in the ^{18}FDG-PET signal of up to 20%, the drug group showed no reduction at all and even demonstrated improved signalling in some brain areas [93] (NCT01469351).

A second larger scale phase II clinical trial with liraglutide in 206 MCI patients is currently ongoing in the UK. The trial has a randomised, placebo controlled double blind design and will analyse ^{18}FDG-PET brain activity, PET inflammation markers (microglia activation), MRI brain scan changes, CSF samples for inflammation markers and amyloid /tau levels, and cognitive tests such as the ADAS Exec score. Patient recruitment is currently ongoing (NCT01843075).

References:

1. Moroo I, Yamada T, Makino H, et al. Loss of insulin receptor immunoreactivity from the substantia nigra pars compacta neurons in Parkinson's disease. Acta Neuropathol (Berl) 1994;87:343-8.

2. Aviles-Olmos I, Limousin P, Lees A, Foltynie T. Parkinson's disease, insulin resistance and novel agents of neuroprotection. Brain : a journal of neurology 2013;136:374-84.
3. Strachan MW. Insulin and cognitive function in humans: experimental data and therapeutic considerations. Biochemical Society transactions 2005;33:1037-40.
4. Haan MN. Therapy Insight: type 2 diabetes mellitus and the risk of late-onset Alzheimer's disease. Nat Clin Pract Neurol 2006;2:159-66.
5. Luchsinger JA, Tang MX, Shea S, Mayeux R. Hyperinsulinemia and risk of Alzheimer disease. Neurology 2004;63:1187-92.
6. Ristow M. Neurodegenerative disorders associated with diabetes mellitus. J Mol Med 2004;82:510-29.
7. Biessels GJ, De Leeuw FE, Lindeboom J, Barkhof F, Scheltens P. Increased cortical atrophy in patients with Alzheimer's disease and type 2 diabetes mellitus. Journal of neurology, neurosurgery, and psychiatry 2006;77:304-7.
8. Leibson CL, Rocca WA, Hanson VA, et al. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. American journal of epidemiology 1997;145:301-8.
9. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of type 2 diabetes in Alzheimer disease. Diabetes 2004;53:474-81.
10. Ohara T, Doi Y, Ninomiya T, et al. Glucose tolerance status and risk of dementia in the community: The Hisayama Study. Neurology 2011;77:1126-34.
11. Schrijvers EM, Witteman JC, Sijbrands EJ, Hofman A, Koudstaal PJ, Breteler MM. Insulin metabolism and the risk of Alzheimer disease: the Rotterdam Study. Neurology 2010;75:1982-7.
12. Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. Diabetes care 2007;30:842-7.
13. Cereda E, Barichella M, Cassani E, Caccialanza R, Pezzoli G. Clinical features of Parkinson disease when onset of diabetes came first: A case-control study. Neurology 2012;78:1507-11.
14. Cereda E, Barichella M, Pedrolli C, et al. Diabetes and risk of Parkinson's disease: a systematic review and meta-analysis. Diabetes care 2011;34:2614-23.
15. Lu L, Fu DL, Li HQ, Liu AJ, Li JH, Zheng GQ. Diabetes and risk of Parkinson's disease: an updated meta-analysis of case-control studies. PloS one 2014;9:e85781.
16. Lima MM, Targa AD, Noseda AC, et al. Does Parkinson's disease and type-2 diabetes mellitus present common pathophysiological mechanisms and treatments? CNS & neurological disorders drug targets 2014;13:418-28.
17. Steen E, Terry BM, Rivera E, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease - is this type 3 diabetes? Journal of Alzheimer's disease : JAD 2005;7:63-80.
18. Lester-Coll N, Rivera EJ, Soscia SJ, Doiron K, Wands JR, de la Monte SM. Intracerebral streptozotocin model of type 3 diabetes: relevance to sporadic Alzheimer's disease. Journal of Alzheimer's disease : JAD 2006;9:13-33.
19. Talbot K, Wang HY, Kazi H, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. The Journal of clinical investigation 2012;122:1316-38.
20. Moloney AM, Griffin RJ, Timmons S, O'Connor R, Ravid R, O'Neill C. Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. Neurobiology of aging 2010;31:224-43.

21. Morris JK, Zhang H, Gupte AA, Bomhoff GL, Stanford JA, Geiger PC. Measures of striatal insulin resistance in a 6-hydroxydopamine model of Parkinson's disease. Brain research 2008;1240:185-95.
22. Pellecchia MT, Santangelo G, Picillo M, et al. Insulin-like growth factor-1 predicts cognitive functions at 2-year follow-up in early, drug-naive Parkinson's disease. European journal of neurology : the official journal of the European Federation of Neurological Societies 2014;21:802-7.
23. Morris JK, Bomhoff GL, Gorres BK, et al. Insulin resistance impairs nigrostriatal dopamine function. Experimental neurology 2011;231:171-80.
24. Numao A, Suzuki K, Miyamoto M, Miyamoto T, Hirata K. Clinical correlates of serum insulin-like growth factor-1 in patients with Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. Parkinsonism & related disorders 2014;20:212-6.
25. Banks WA. The source of cerebral insulin. European journal of pharmacology 2004;490:5-12.
26. Fernando RN, Albiston AL, Chai SY. The insulin-regulated aminopeptidase IRAP is colocalised with GLUT4 in the mouse hippocampus--potential role in modulation of glucose uptake in neurones? The European journal of neuroscience 2008;28:588-98.
27. Ghasemi R, Haeri A, Dargahi L, Mohamed Z, Ahmadiani A. Insulin in the brain: sources, localization and functions. Molecular neurobiology 2013;47:145-71.
28. Carro E, Torres-Aleman I. The role of insulin and insulin-like growth factor I in the molecular and cellular mechanisms underlying the pathology of Alzheimer's disease. European journal of pharmacology 2004;490:127-33.
29. Craft S, Cholerton B, Baker LD. Insulin and Alzheimer's disease: untangling the web. Journal of Alzheimer's disease : JAD 2013;33 Suppl 1:S263-75.
30. Hoyer S. Glucose metabolism and insulin receptor signal transduction in Alzheimer disease. European journal of pharmacology 2004;490:115-25.
31. Holscher C. Insulin, incretins and other growth factors as potential novel treatments for Alzheimer's and Parkinson's diseases. Biochemical Society transactions 2014;42:593-9.
32. Watson GS, Craft S. Modulation of memory by insulin and glucose: neuropsychological observations in Alzheimer's disease. European journal of pharmacology 2004;490:97-113.
33. Zhao WQ, Chen H, Quon MJ, Alkon DLw. Insulin and the insulin receptor in experimental models of learning and memory. European journal of pharmacology 2004;490:71-81.
34. Reger MA, Watson GS, Green PS, et al. Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. Journal of Alzheimer's disease : JAD 2008;13:323-31.
35. Okereke OI, Selkoe DJ, Pollak MN, et al. A profile of impaired insulin degradation in relation to late-life cognitive decline: A preliminary investigation. Int J Geriatr Psychiatry 2008;24:177-82.
36. Reger MA, Watson GS, Green PS, et al. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology 2008;70:440-8.
37. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Current Alzheimer research 2007;4:147-52.
38. Craft S. A randomized, placebo-controlled trial of intranasal insulin in amnestic MCI and early Alzheimer's. ICAD conference. Hawaii, USA, d2010:abstr. P3-455.
39. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Archives of neurology 2012;69:29-38.

40. Claxton A, Baker LD, Hanson A, et al. Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. Journal of Alzheimer's disease : JAD 2015;44:897-906.
41. Freiherr J, Hallschmid M, Frey WH, 2nd, et al. Intranasal insulin as a treatment for Alzheimer's disease: a review of basic research and clinical evidence. CNS drugs 2013;27:505-14.
42. Holscher C. First clinical data of the neuroprotective effects of nasal insulin application in patients with Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 2014;10:S33-S7.
43. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007;132:2131-57.
44. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. Cell metabolism 2013;17:819-37.
45. Lean ME, Carraro R, Finer N, et al. Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. Int J Obes (Lond) 2014;38:689-97.
46. Baggio LL, Kim JG, Drucker DJ. Chronic exposure to GLP-1R agonists promotes homologous GLP-1 receptor desensitization in vitro but does not attenuate GLP-1R-dependent glucose homeostasis in vivo. Diabetes 2004;53 Suppl 3:S205-14.
47. Banks WA, Jaspan JB, Kastin AJ. Selective, physiological transport of insulin across the blood-brain barrier: novel demonstration by species-specific radioimmunoassays. Peptides 1997;18:1257-62.
48. Kastin AJ, Akerstrom V, Pan W. Interactions of glucagon-like peptide-1 (GLP-1) with the blood-brain barrier. Journal of molecular neuroscience : MN 2002;18:7-14.
49. Kastin AJ, Akerstrom V. Entry of exendin-4 into brain is rapid but may be limited at high doses. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 2003;27:313-8.
50. Hunter K, Holscher C. Drugs developed to treat diabetes, liraglutide and lixisenatide, cross the blood brain barrier and enhance neurogenesis. BMC neuroscience 2012;13:33-8.
51. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. The Journal of clinical investigation 2014;124:4473-88.
52. Merchenthaler I, Lane M, Shughrue P. Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. The Journal of comparative neurology 1999;403:261-80.
53. Teramoto S, Miyamoto N, Yatomi K, et al. Exendin-4, a glucagon-like peptide-1 receptor agonist, provides neuroprotection in mice transient focal cerebral ischemia. J Cereb Blood Flow Metab 2011;31:1696-705.
54. Darsalia V, Ortsäter H, Olverling A, et al. The DPP-4 inhibitor linagliptin counteracts stroke in the normal and diabetic mouse brain: a comparison with glimepiride. Diabetes 2013;62:1289-96.
55. Darsalia V, Mansouri S, Ortsater H, et al. Glucagon-like peptide-1 receptor activation reduces ischaemic brain damage following stroke in Type 2 diabetic rats. Clin Sci (Lond) 2012;122:473-83.
56. Lee CH, Yan B, Yoo KY, et al. Ischemia-induced changes in glucagon-like peptide-1 receptor and neuroprotective effect of its agonist, exendin-4, in experimental transient cerebral ischemia. Journal of neuroscience research 2011;89:1103-13.
57. During MJ, Cao L, Zuzga DS, et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nature medicine 2003;9:1173-9.

58. Hamilton A, Holscher C. Receptors for the insulin-like peptide GLP-1 are expressed on neurons in the CNS. Neuroreport 2009;20:1161-6.
59. Li Y, Perry T, Kindy MS, et al. GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. Proceedings of the National Academy of Sciences of the United States of America 2009;106:1285-90.
60. Drucker DJ. Incretin action in the pancreas: potential promise, possible perils, and pathological pitfalls. Diabetes 2013;62:3316-23.
61. Cork SC, Richards JE, Holt MK, Gribble FM, Reimann F, Trapp S. Distribution and characterisation of Glucagon-like peptide-1 receptor expressing cells in the mouse brain. Mol Metab 2015;4:718-31.
62. Courreges JP, Vilsboll T, Zdravkovic M, et al. Beneficial effects of once-daily liraglutide, a human glucagon-like peptide-1 analogue, on cardiovascular risk biomarkers in patients with Type 2 diabetes. Diabetic medicine : a journal of the British Diabetic Association 2008;25:1129-31.
63. McClean P, Parthsarathy V, Faivre E, Hölscher C. The diabetes drug Liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. The Journal of neuroscience : the official journal of the Society for Neuroscience 2011;31:6587-94.
64. McClean PL, Holscher C. Liraglutide can reverse memory impairment, synaptic loss and reduce plaque load in aged APP/PS1 mice, a model of Alzheimer's disease. Neuropharmacology 2014;76 Pt A:57-67.
65. McClean PL, Jalewa J, Holscher C. Prophylactic liraglutide treatment prevents amyloid plaque deposition, chronic inflammation and memory impairment in APP/PS1 mice. Behavioural brain research 2015;293:96-106.
66. McClean PL, Holscher C. Lixisenatide, a drug developed to treat type 2 diabetes, shows neuroprotective effects in a mouse model of Alzheimer's disease. Neuropharmacology 2014;86C:241-58.
67. Hansen HH, Barkholt P, Fabricius K, et al. The GLP-1 receptor agonist liraglutide reduces pathology-specific tau phosphorylation and improves motor function in a transgenic hTauP301L mouse model of tauopathy. Brain research 2015;1634:158-70.
68. Hansen HH, Fabricius K, Barkholt P, et al. The GLP-1 Receptor Agonist Liraglutide Improves Memory Function and Increases Hippocampal CA1 Neuronal Numbers in a Senescence-Accelerated Mouse Model of Alzheimer's Disease. Journal of Alzheimer's disease : JAD 2015.
69. Li Y, Duffy K, Ottinger M, et al. GLP-1 Receptor Stimulation Reduces Amyloid-beta Peptide Accumulation and Cytotoxicity in Cellular and Animal Models of Alzheimer's Disease. Journal of Alzheimer's disease : JAD 2010;19:1205-19.
70. Perry T, Greig NH. Enhancing central nervous system endogenous GLP-1 receptor pathways for intervention in Alzheimer's disease. Current Alzheimer research 2005;2:377-85.
71. Rachmany L, Tweedie D, Li Y, et al. Exendin-4 induced glucagon-like peptide-1 receptor activation reverses behavioral impairments of mild traumatic brain injury in mice. Age (Dordr) 2012.
72. Eakin K, Li Y, Chiang YH, et al. Exendin-4 ameliorates traumatic brain injury-induced cognitive impairment in rats. PloS one 2013;8:e82016.
73. Perry T, Holloway HW, Weerasuriya A, et al. Evidence of GLP-1-mediated neuroprotection in an animal model of pyridoxine-induced peripheral sensory neuropathy. Experimental neurology 2007;203:293-301.

74. Porter DW, Irwin N, Flatt PR, Holscher C, Gault VA. Prolonged GIP receptor activation improves cognitive function, hippocampal synaptic plasticity and glucose homeostasis in high-fat fed mice. European journal of pharmacology 2010;650:688-93.
75. Porter DW, Kerr BD, Flatt PR, Holscher C, Gault VA. Four weeks administration of Liraglutide improves memory and learning as well as glycaemic control in mice with high fat dietary-induced obesity and insulin resistance. Diabetes, obesity & metabolism 2010;12:891-9.
76. Hamilton A, Patterson S, Porter D, Gault VA, Holscher C. Novel GLP-1 mimetics developed to treat type 2 diabetes promote progenitor cell proliferation in the brain. Journal of neuroscience research 2011;89:481-9.
77. Faivre E, Holscher C. D-Ala2GIP facilitated synaptic plasticity and reduces plaque load in aged wild type mice and in an Alzheimer's disease mouse model. Journal of Alzheimer's disease : JAD 2013;35:267-83.
78. Faivre E, Holscher C. Neuroprotective effects of D-Ala2GIP on Alzheimer's disease biomarkers in an APP/PS1 mouse model. Alzheimer's research & therapy 2013;5:20-8.
79. Duffy AM, Holscher C. The incretin analogue D-Ala(2)GIP reduces plaque load, astrogliosis and oxidative stress in an APP/PS1 mouse model of Alzheimer's disease. Neuroscience 2013;228:294-300.
80. Bertilsson G, Patrone C, Zachrisson O, et al. Peptide hormone exendin-4 stimulates subventricular zone neurogenesis in the adult rodent brain and induces recovery in an animal model of Parkinson's disease. Journal of neuroscience research 2008;86:326-38.
81. Harkavyi A, Abuirmeileh A, Lever R, Kingsbury AE, Biggs CS, Whitton PS. Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease. Journal of neuroinflammation 2008;5:19(1-9).
82. Liu W, Jalewa J, Sharma M, Li G, Li L, Hölscher C. Neuroprotective effects of lixisenatide and liraglutide in the MPTP mouse model of Parkinson's disease. Neuroscience 2015;303:42-50.
83. Li Y, Liu W, Li L, Holscher C. Neuroprotective effects of a GIP analogue in the MPTP Parkinson's disease mouse model. Neuropharmacology 2015;101:255-63.
84. Finan B, Ma T, Ottaway N, et al. Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. Science translational medicine 2013;5:209ra151.
85. Ji C, Xue GF, Lijun C, et al. A novel dual GLP-1 and GIP receptor agonist is neuroprotective in the MPTP mouse model of Parkinson's disease by increasing expression of BNDF. Brain research 2015;DOI: 10.1016/j.brainres.2015.09.035.
86. Cao L, Li D, Feng P, et al. A novel dual GLP-1 and GIP incretin receptor agonist is neuroprotective in a mouse model of Parkinson's disease by reducing chronic inflammation in the brain. Neuroreport 2016;DOI:10.1097/WNR.0000000000000548.
87. Blurton-Jones M, Kitazawa M, Martinez-Coria H, et al. Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. Proceedings of the National Academy of Sciences of the United States of America 2009;106:13594-9.
88. Allen SJ, Watson JJ, Shoemark DK, Barua NU, Patel NK. GDNF, NGF and BDNF as therapeutic options for neurodegeneration. Pharmacology & therapeutics 2013;138:155-75.
89. Aviles-Olmos I, Dickson J, Kefalopoulou Z, et al. Exenatide and the treatment of patients with Parkinson's disease. The Journal of clinical investigation 2013;123:2730-6.
90. Aviles-Olmos I, Dickson J, Kefalopoulou Z, et al. Motor and Cognitive Advantages Persist 12 Months After Exenatide Exposure in Parkinson's Disease. Journal of Parkinson's disease 2014;4:337-44.

91. Egefjord L, Gejl M, Moller A, et al. Effects of liraglutide on neurodegeneration, blood flow and cognition in Alzheimer s disease - protocol for a controlled, randomized double-blinded trial. Danish medical journal 2012;59:A4519.
92. Femminella GD, Edison P. Evaluation of neuroprotective effect of glucagon-like peptide 1 analogs using neuroimaging. Alzheimer's & dementia : the journal of the Alzheimer's Association 2014;10:S55-61.
93. Gejl M, Gjedde A, Egefjord L, et al. In Alzheimer's Disease, Six-Month Treatment with GLP-1 Analogue Prevents Decline of Brain Glucose Metabolism: Randomized, Placebo-Controlled, Double-Blind Clinical Trial. Frontiers in aging neuroscience 2016;DOI:10.3389/fnagi.2016.00108.

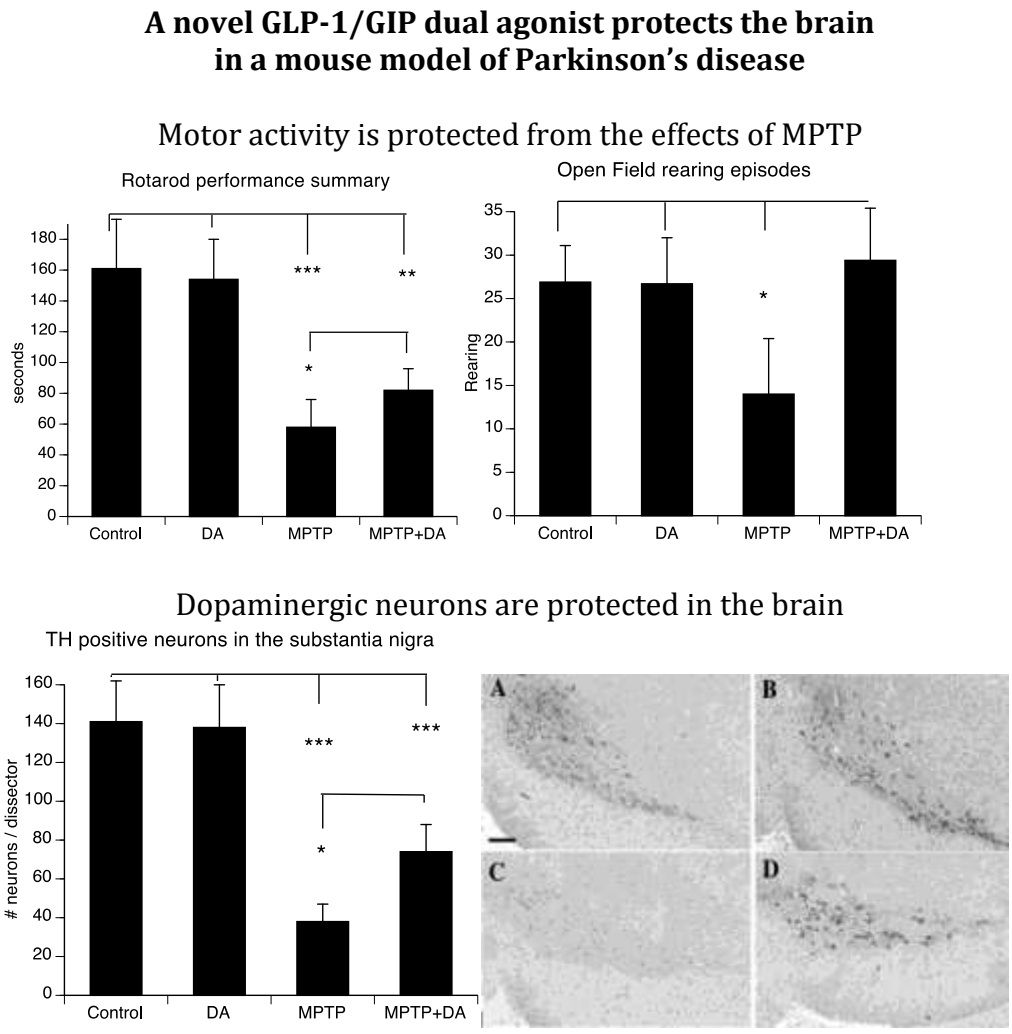

Fig. 1: A novel dual GLP-1 and GIP receptor agonist displays neuroprotective properties in the MPTP mouse model of PD. Motor activity was much reduced by MPTP, and the novel drug rescued this to some extent. In the substantia nigra, dopaminergic neurons that express TH are much reduced in numbers by MPTP, and the novel dual agonist protected neurons to some extend. Shown are histological sample sections; A=saline control, B=drug, C=MPTP, D=MPTP plus drug. Adapted from [86].